# Paclitaxel

**Brand Name: Taxol, Onxol**
**Drug Class: Opportunistic Infection and Other Drugs**

## Drug Description

Paclitaxel is a natural or semi-synthetic antineoplastic diterpene extracted from the bark of the Western (Pacific) yew (Taxus brevifolia) or from needles and twigs of a more prevalent yew (Taxus baccata). [1]

## HIV/AIDS-Related Uses

Paclitaxel was approved by the FDA on August 4, 1997 for use as second-line treatment of AIDS-related Kaposi's sarcoma (KS).[2]

Use of a liposomal anthracycline (doxorubicin or daunorubicin) is currently the first-line therapy of choice for advanced AIDS-related KS. Although the comparative efficacy of paclitaxel versus other treatments for advanced AIDS-related KS has not been established, paclitaxel has shown substantial activity in patients with advanced disease (e.g., extensive mucocutaneous disease, lymphedema, symptomatic visceral disease). Objective responses to paclitaxel therapy have been reported in patients with poor prognostic factors, including low baseline helper/inducer T cell counts, visceral involvement, or history of opportunistic infection, as well as in patients who have received prior systemic chemotherapy. However, the depressed immunologic status of these patients limits the therapeutic benefit of systemic chemotherapy, and there currently are no data showing unequivocal evidence of improved survival with any treatment for AIDS-related KS.[3]

## Non-HIV/AIDS-Related Uses

Paclitaxel is used alone and in combination therapy for the treatment of ovarian cancer. Its use is indicated for first-line (with cisplatin) and subsequent therapy for treatment of advanced ovarian carcinoma; for adjuvant treatment of node-positive breast cancer when administered sequentially to standard doxorubicin-containing combination chemotherapy; for treatment of metastatic breast carcinoma after failure of combination chemotherapy or at relapse within 6 months of adjuvant chemotherapy; and for first-line treatment of non-small cell lung carcinoma in patients who are not candidates for radiation therapy or potentially curative surgery.[4]

## Pharmacology

Paclitaxel belongs to the class of medications known as antimicrotubule agents. It promotes microtubule assembly from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of normal dynamic reorganization of the microtubule network that is essential for progression through the cell cycle. In addition, paclitaxel induces abnormal arrays of "bundles" of microtubules throughout the cell cycle along with multiple asters of microtubules during mitosis.[5] Evidence suggests that paclitaxel may also induce cell death by triggering apoptosis; paclitaxel also enhances the cytotoxic effects of ionizing radiation in vitro.[6]

Peak plasma concentrations of paclitaxel following intravenous (IV) administration exhibit marked interindividual variation. Plasma concentrations of paclitaxel increase during continuous IV administration of the drug and decline immediately following completion of infusion. Following 24-hour IV infusion of paclitaxel at doses of 135 mg/m2 to 175 mg/m2 in patients with advanced ovarian cancer, peak plasma concentrations (Cmax) averaged 195 ng/ml or 365 ng/ml, respectively. The increase in dose (30%) was associated with a disproportionately greater increase in Cmax (87%).[7]

Paclitaxel is widely distributed into body fluids and tissues after IV administration. Paclitaxel has a large volume of distribution that appears to be affected by dose and duration of infusion. Following administration of paclitaxel doses of 135 mg/m2 to 175 mg/m2 by IV infusion over 24 hours in patients with advanced ovarian cancer, the mean apparent volume of distribution at steady state ranged from 227 to 688 L/m2. Paclitaxel does not appear to readily penetrate the central nervous system, but paclitaxel has been detected in ascitic fluid following IV infusion. It is not known if paclitaxel distributes into human milk, but in lactating rats given radiolabeled paclitaxel,

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## Pharmacology (cont.)

concentrations of radioactivity in milk were higher than those in plasma and declined in parallel with plasma concentrations of the drug.[8]

Paclitaxel is in FDA Pregnancy Category D. Adequate and well-controlled studies have not been done in pregnant women. Studies in rats at doses of 1 mg per kg of body weight found that paclitaxel reduced fertility. It is usually recommended that the use of antineoplastics, especially combination chemotherapy, be avoided whenever possible in pregnant women, especially during the first trimester. Although information is limited because of the relatively few instances of antineoplastic administration during pregnancy, the mutagenic, teratogenic, and carcinogenic potential of these medications must be considered. Hazards to the fetus include adverse reactions seen in adults. Paclitaxel was found to cause maternal and embryo-fetal toxicity in rabbits at intravenous doses of 3 mg/kg given during organogenesis. In rats and rabbits, paclitaxel was found to cause abortions, decreased corpora lutea, a decrease in implantations and live fetuses, and increased resorptions and embryo-fetal deaths. No gross external, soft tissue, or skeletal alterations have been observed.[9]

At plasma concentrations ranging from 0.1 mcg/ml to 50 mcg/ml, 88% to 98% of paclitaxel is bound to plasma proteins. Following IV infusion of paclitaxel over periods ranging from 6 to 24 hours in adults with malignancy, plasma concentrations of paclitaxel appear to decline in a biphasic manner in some studies, with an average distribution half-life of 0.34 hours and an average elimination half-life of 5.8 hours. However, additional studies, particularly those in which paclitaxel is administered over a shorter period of infusion, show that the drug exhibits nonlinear pharmacokinetic behavior. In patients receiving paclitaxel 175 mg/m2 administered by 3-hour IV infusion, the distribution half-life averages 0.27 hours and the elimination half-life averages 2.33 hours.[10]

Paclitaxel is extensively metabolized in the liver by the isoenzymes CYP2C8 and CYP3A4. Paclitaxel and its metabolites are principally excreted in the feces via biliary elimination with minimal urinary excretion; unchanged drug in urine typically accounts for less than 10% of an administered dose. Hemodialysis only minimally removes paclitaxel. Administration of cisplatin followed by paclitaxel decreases paclitaxel clearance by 25% to 33%. When cisplatin and paclitaxel must be administered sequentially, the sequence of paclitaxel followed by cisplatin is recommended.[11]

## Adverse Events/Toxicity

Adverse effects observed with the use of paclitaxel include anemia; hypersensitivity reaction; leukopenia or neutropenia, with or without infection; thrombocytopenia; cardiovascular effects, including bradycardia, hypotension, or abnormal electrocardiogram (ECG); elevated serum hepatic enzymes; arthralgias or myalgias; diarrhea; nausea or vomiting; peripheral neuropathy, including mild paresthesia; and alopecia.[12]

## Drug and Food Interactions

Concomitant administration of central nervous system (CNS) depressants (e.g., antihistamines, opiates) with paclitaxel should be undertaken with caution as these drugs may cause potentiation of CNS depression caused by the alcohol contained in the paclitaxel formulation. Concomitant administration of drugs that affect cytochrome P-450 (CYP) hepatic microsomal enzymes could alter the metabolism of paclitaxel, although specific studies have not been performed and the clinical importance has not been determined. Metabolism of paclitaxel is mediated by CYP2C8 and CYP3A4, and the possibility exists that drugs that induce these isoenzymes may reduce plasma paclitaxel concentrations. Conversely, concomitant administration of paclitaxel with drugs that inhibit these isoenzymes may increase plasma paclitaxel concentrations, and drugs that are metabolized by the isoenzymes may have decreased metabolism because of competition for the enzymes. Patients receiving such therapy should be monitored for toxicities associated with the drug and for inadequate response to any of the drugs.[13]

Concurrent use of bone marrow depressants and radiation therapy with paclitaxel may cause additive bone marrow depression. Dosage

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## Drug and Food Interactions (cont.)

reduction may be required when two or more bone marrow depressants, including radiation, are used concurrently or consecutively. Severity of paclitaxel-induced neutropenia may be related to the extent of prior myelotoxic therapy.[14] Sequence-dependent drug interactions have been reported to occur when paclitaxel is administered with other antineoplastic agents, including cisplatin, doxorubicin, and cyclophosphamide.[15]

Because normal defense mechanisms may be suppressed by paclitaxel therapy, concurrent use with a live virus vaccine may potentiate the replication of the vaccine virus, may increase the side/adverse effects of the vaccine virus, and/or may decrease the patient's antibody response to the vaccine. Immunization of patients taking paclitaxel should be undertaken only with extreme caution after careful review of the patient's hematologic status and only with the knowledge and consent of the physician managing the paclitaxel therapy.[16]

## Contraindications

Paclitaxel for injection should not be used in patients with known severe hypersensitivity to the polyoxyl 35 castor oil vehicle or to the drug.[17]

Risk-benefit assessment should be considered in patients with bone marrow depression; cardiac function impairment, including angina and cardiac conduction abnormalities; history of congestive heart failure or myocardial infarction within the past 6 months; existing or recent onset or exposure to chickenpox or herpes zoster; infection; or previous cytotoxic drug therapy or radiation therapy. It is recommended that paclitaxel not be administered to patients with AIDS-associated KS when baseline neutrophil counts are lower than 1000 cells/mm3 because use of paclitaxel will further bone marrow depression.[18]

## Clinical Trials

For information on clinical trials that involve Paclitaxel, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Paclitaxel AND HIV Infections.

## Dosing Information

Mode of Delivery: Intravenous.[19]

Dosage Form: Paclitaxel for injection in 5 ml vials with equivalent of 30 mg paclitaxel; 16.7 ml vials with equivalent of 100 mg paclitaxel; 50 ml vials with equivalent of 300 mg paclitaxel.[20]

Storage: Vials of paclitaxel should be stored between 20 C and 25 C (68 F to 77 F).[21]

## Chemistry

CAS Name: Benzenepropanoic acid, beta-(benzoylamino)-alpha-hydroxy-,6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca(3,4)benz(1,2-b)oxet-9-ylester,(2aR-(2aalpha,4beta,4abeta,6beta,9alpha(alphaR*,betaS*),11alpha,1-2alpha,12a-alpha,12b-alpha))-[22]

CAS Number: 33069-62-4[23]

Molecular formula: C47-H51-N-O14[24]

C66.11%, H6.02%, N1.64%, O26.23%[25]

Molecular weight: 853.90[26]

Melting point: 213 to 216 C[27]

Physical Description: Paclitaxel is highly lipophilic and insoluble in water.[28]

Stability: Unopened vials of paclitaxel injection are stable until the date indicated on the package when stored between 20 C and 25 C (68 F to 77 F) in the original package. Neither freezing nor refrigeration adversely affects the stability of the product. Upon refrigeration, components in the vial may precipitate, but will redissolve upon reaching room temperature with little or no agitation. If the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded. Solutions for infusion prepared as recommended are stable at ambient temperatures (approximately 25 C) and lighting conditions for up to 27 hours.[29]

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## Other Names

Taxol A[30]

Paxene[31]

## Further Reading

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Dezube BJ. Management of AIDS-related Kaposi's sarcoma: advances in target discovery and treatment. Expert Rev Anticancer Ther. 2002 Apr;2(2):193-200. Review. PMID: 12113241

Levine AM, Tulpule A. Clinical aspects and management of AIDS-related Kaposi's sarcoma. Eur J Cancer. 2001 Jul;37(10):1288-95. Review. PMID: 11423260

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Tulpule A, Groopman J, Saville MW, Harrington W Jr, Friedman-Kien A, Espina BM, Garces C, Mantelle L, Mettinger K, Scadden DT, Gill PS. Multicenter trial of low-dose paclitaxel in patients with advanced AIDS-related Kaposi sarcoma. Cancer. 2002 Jul 1;95(1):147-54. PMID: 12115328

## Manufacturer Information

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IVAX Pharmaceuticals Inc.
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(800) 321-1335

Taxol
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## For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

## References


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3. AHFS Drug Information - 2003; p. 1099

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5. USP DI - 2003; p. 2120

6. AHFS Drug Information - 2003; p. 1106

7. AHFS Drug Information - 2003; p. 1106

8. AHFS Drug Information - 2003; p. 1106

9. USP DI - 2003; p. 2120

10. AHFS Drug Information - 2003; p. 1106

11. AHFS Drug Information - 2003; p. 1106

12. USP DI - 2003; p. 2121-2122

13. AHFS Drug Information - 2003; p. 1105

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16. USP DI - 2003; p. 2121

17. AHFS Drug Information - 2003; p. 1105

18. USP DI - 2003; p. 2121

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20. Bristol-Myers Squibb - Taxol - Patient Information, p. 6. Available at: http://www.taxol.com/txpi.html. Accessed 09/29/03.

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